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Cellular Functions of ER Chaperones in Regulating Protein Misfolding and Aggregation: An Emerging Therapeutic Approach for Preeclampsia

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Abstract

Proteinuria is one of the hallmarks of preeclampsia (PE) that differentiates other hypertensive disorders of pregnancy. Protein misfolding and aggregation is an emerging pathological condition underlying many chronic metabolic diseases and neurodegenerative diseases. Recent studies indicate protein aggregation as an emerging biomarker of preeclampsia, wherein several proteins are aggregated and dysregulated in the body fluids of preeclamptic women, provoking the multi-systemic clinical manifestations of the disease. At the cellular level, these misfolded and aggregated proteins are potentially toxic interfering with the normal physiological process, eliciting the unfolded protein response (UPR) pathway activators in the endoplasmic reticulum (ER) that subsequently augments the ER quality control systems to remove these aberrant proteins. ER resident chaperones, folding enzymes and other proteins serve as part of the ER quality control machinery in restoring nascent protein folding. These ER chaperones are crucial for ER function aiding in native protein folding, maintaining calcium homeostasis, as sensors of ER stress and also as immune modulators. Consequently, ER chaperones seems to be involved in many cellular processes, yet the association is expanding to be explored. Understanding the role and mechanism of ER chaperones in regulating protein misfolding and aggregation would provide new avenues for therapeutic intervention as well as for the development of new diagnostic approaches.

Keywords: ER stress, ER chaperone, protein misfolding, aggregation, preeclampsia

1. Introduction

Hypertensive disorders are a most common medical problem encountered during pregnancy, affecting 6–8% of all pregnancies. Approximately 70% of hypertensive disorders in pregnancy are mainly due to gestational hypertension, adding up further complications. Preeclampsia (PE) is a multi-systemic disease diagnosed by the presence of new onset hypertension accompanied by proteinuria,

renal insufficiency, pulmonary edema, liver failure, neurological complications and fetal growth restriction [1]. The progression of the disease is unpredictable mainly leading to fetal damage associated with other clinical manifestations such as thrombocytopenia, oxidative stress, vascular endothelial dysfunction, systemic inflammation and aberrant angiogenesis, which invariably necessitates early diagnosis of the disease condition so as to prevent further pathogenesis [2].

Proteinuria is one of the hallmarks of preeclampsia that differentiates it from other hypertensive disorders of pregnancy. Recent studies have indicated that protein aggregation as an emerging biomarker of PE, providing insights for therapeutic intervention and development of new diagnostic approaches. Notably, endoplasmic reticulum (ER) stress has recently emerged as a major pathological condition underlying chronic metabolic diseases such as diabetes, cancer, neurodegenerative diseases including PE. At the cellular level, misfolded proteins in the ER significantly lead to ER stress by activating the unfolded protein response (UPR) pathway and molecular chaperones [3–8]. Mis-folded or aggregated proteins are potentially cytotoxic, and consequently cells possess quality control systems to remove these aberrant proteins. These aberrant proteins will expose hydrophobic regions, free cysteines and tend to aggregate, molecular chaperones play key roles in ER quality control because they recognize mis-folded and aggregation-prone proteins [9, 10]. ER chaperones, folding enzymes and other proteins involved in ER stress would serve as a valuable tool in the investigation of disease pathogenesis, prediction of early diagnostic markers and development of targeted therapies. Hence, exploring the structure and functions of ER chaperones would provide new insights in reducing the cellular stress underlying preeclampsia.

2. Regulation of ER stress

Endoplasmic reticulum (ER) is a cellular organelle involved in multiple cellular processes required for cell survival and physiological functions. These processes include intracellular calcium homeostasis, protein secretion and lipid biosynthesis [11–13]. ER constantly monitors the level and conformational status of secreted and membrane-related proteins and rapidly activates multiple signaling pathways in response to changes in the quality and quantity of the proteins it processes, levels of reactive oxygen species and metabolic changes. The ER has a specialized environment, including complexes of chaperones and foldases, as well as high fidelity quality controlling mechanisms to ensure the crucial maintenance of ER homeostasis in cells. ER homeostasis is a unique equilibrium between the cellular demand for protein synthesis and the ER folding capacity to promote protein transportation and maturation.

The ER lumen is a one-of-a-kind biological environment, wherein cells are flooded with calcium in order to mediate the active transport of proteins by calcium ATPases. In addition, ER is also concentrated in calcium-dependent chaperones such as glucose-regulated protein, 78 kDa (GRP78), GRP94 and calreticulin, which help in stabilizing protein-folding intermediates. The oxidative environment in the ER lumen is crucial for disulphide bond formation mediated by protein disulphide isomerase (PDI). The di-sulfide bond formation helps in the proper folding of many proteins intended for secretion as well as those expressed on the cell surface. Different post-translational modifications, including glycosylation and lipidation of proteins too occur in the ER [14, 15].

Disparity in ER function leads to a state known as ER stress, which activates a series of evolutionarily conserved signaling pathways collectively referred to as the unfolded protein response (UPR). Triggering of UPR pathways results in three

effector functions: adaptation, alarm and apoptosis [16]. Initially the UPR pathway intends to recover the homeostasis and normalize the ER function. The adaptive mechanism is primarily involved in the activation of transcriptional pathways responsible for enhancing the protein folding capacity and ER-assisted degradation (ERAD). Both of these pathways reduce the load of misfolded proteins in ER by refolding the proteins or exporting them to cytosol for degradation. Initial to this, translation of mRNA is inhibited to prevent the entry of the new protein into ER until the activation of genes encoding UPR pathways [17].

3. Unfolded protein response pathway

Accumulation of unfolded proteins trigger an evolutionarily conserved signaling pathway designated as UPR [18, 19]. Three major proteins: inositol requiring enzyme 1 α/β (IRE1), PKR-like ER kinase (PERK), and activating transcription factor 6 α/β (ATF6) are the key UPR signaling activators [20–22]. These activators are capable of retrotrafficking from ER membrane to cytosol by their unique domain organization. They contain 3 domains: an ER luminal domain (LD), a membrane spanning domain and a cytosolic domain. The LD, either directly or indirectly involved in sensing the misfolded proteins [23]. Type I transmembrane proteins PERK and IRE1 α possess the domain structure that is similar as ER luminal domain structures and a cytosolic Ser/Thr kinase domain, whereas type II transmembrane protein ATF6 α contains a cytosolic cyclic AMP response element-binding protein (CREB)-ATF basic leucine zipper domain. UPR pathway activation involves a reduction in protein synthesis, increased protein folding and transport in the ER, an increase in ER-associated protein degradation and autophagy.

After ER is loaded with unfolded proteins, UPR signaling pathways are not simultaneously activated. Primarily ATF6 α and IRE1 α activation occurs, with subsequent activation of PERK during chronic ER stress [5, 6]. ATF6 α and IRE1 α are responsible for the activation of transcriptional pathways that increases the cell's capacity for protein folding, transport and degradation. Adaptive response to the protein misfolding is achieved by ATF6 α , which is synthesized as an inactive precursor. The N-terminus is located in cytoplasm and serve as an effector portion which possess DNA-binding and transcriptional activation regions. On the accumulation of unfolded protein in ER, ATF6 α travels to the Golgi, and the N-terminal effector portion present in cytosol-bZIP transcription factor is fragmented by S1P and S2P [24]. The fragment induces the genes encoding protein chaperones such as binding immunoglobulin protein (BiP), ER protein 57 (ERp57) and glucose-regulated protein 94 (GRP94), proteins involved in ERAD pathway.

X-box binding protein 1 (XBP1), a transcription factor regulating UPR-associated genes is activated by IRE1 [25, 26]. IRE1 acts as an endonuclease and selectively cleaves the 26-nucleotides from the XBP1u mRNA producing XBP1 spliced mRNA (XBP1s). Activated XBP1s enhances the expression of ER chaperone GRP78, increases the phospholipid biosynthesis and also promotes degradation pathways. Regulated IRE1-dependent decay (RIDD) is also mediated by the activation of IRE1 α when the ER protein-folding load is intolerable [27–29]. PERK-eIF2 α -ATF4 mediated pathway attenuates the non-essential protein synthesis and increases the antioxidant defense system. PERK phosphorylates eIF2 α at Ser51 which temporarily stops the initiation of global mRNA translation. In irony, phosphorylated eIF2 α upregulates the translation of mRNA's such as ATF4 to increase the protein transport capacity in the ER [30]. Genes encoding ER chaperone protein, folding enzymes and genes encoding ERAD system are activated by p-eIF2 α . The collective activation of the genes leads to revive the ER homeostasis

Figure 1.
ER chaperones mediate Protein folding, Quality control, and signaling during ER Stress.

and at saturation, the misfolded proteins are degraded by ERAD system assisted by proteasome mediated degradation and pro-apoptotic protein C/EBP homologous protein (CHOP) [31, 32]. Aforementioned pathways are activated based on the severity of the stress condition (**Figure 1**) [18, 33].

4. Protein misfolding and aggregation

Protein misfolding, aggregation and tissue deposition of fibrous protein aggregates are the critical etiological manifestations of many neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, etc. Recent

studies report that numerous aggregated proteins considerably contributes to the heterogeneous clinical manifestations in preeclamptic women, indicating that protein aggregation and misfolding does have a correlation with the disease pathogenesis. Numerous proteomic profiling studies of urine, serum and placental samples from preeclamptic women based on MS analysis, has revealed that aggregation of proteins significantly contributes to the PE associated pathogenesis. Several proteins, including amyloid beta peptide, transthyretin, alpha-1 antitrypsin, albumin, IgG k-free light chains, and ceruloplasmin are aggregated in PE, resulting in toxic deposition of amyloid-like aggregates in the placenta and body fluids [34, 35]. In addition, many extracellular chaperones like casein, clusterin, pregnancy zone protein are implicated to be dysregulated in pregnancy, leading to the accumulation of misfolded proteins and disease manifestation. Probably, these aggregated proteins in the early stages of pregnancy induces defective trophoblast invasion, placental ischemia, ER stress thereby promoting PE manifestation. Insights into the molecular mechanisms of formation of these aggregated proteins and understanding the role of molecular chaperones in regulating the misfolded proteins will open new avenues for pharmacological intervention and therapeutic targeting of PE.

Disruption of ER homeostasis as a result of excess accumulation of unfolded/misfolded proteins due to prolonged or severe ER stress is involved in several pathologies that induce endometriosis and endometrial/ovarian cancers as well as various pregnancy complications that result in preeclampsia, fetal growth restriction and preterm birth. Depending on the severity of ER stress, UPR behaves as sort of binary switch between life and death. Initially, the UPR aims to restore ER homeostasis, but if these attempts fail then the apoptotic cascade is activated. These pathways are now recognized as playing a central role in the pathophysiology of chronic diseases, which contributes to the placental pathology in early-onset PE [36].

The ER has tremendous intracellular store of Ca^{2+} necessary for regulating a variety of cellular functions both in the ER lumen and cytosol. Inside the ER lumen, huge reserves of Ca^{2+} are important for proper protein folding assisting disulfide bond forming chaperone, protein disulfide isomerases (PDI). To maintain the ER calcium levels, sarcoendoplasmic reticulum calcium transport ATPase (SERCA) pumps in the ER membrane actively transport Ca^{2+} from the cytosol into the ER lumen. These pumps are specifically regulated based on the proportion of Ca^{2+} in the ER lumen to the cytosol. Alteration in SERCA pumps blocks the movement of Ca^{2+} into the ER, decreasing the function of molecular chaperones and PDI, thereby increasing the burden of misfolded proteins in the ER [37].

5. Pathophysiology of PE

Impaired placentation mainly contributes to the manifestation of systemic symptoms in PE, which may be preceded or followed by protein misfolding and aggregation along with subsequent placental release of inflammatory cytokines, anti-angiogenetic factors, placental debris and particles as well as protein aggregates into the maternal circulation. This pre-clinical dysregulation causes endothelial dysfunction, excessive thrombin generation, systemic inflammation and as a result, elicits multiorgan syndromes of PE [38–41]. During early stages of pregnancy, several proteins such as transthyretin, may be transported to the placenta from maternal circulation. These aggregation-prone proteins easily undergo misfolding and aggregation in the microenvironment of non-compatible conditions, such as acidic pH, ischemia/hypoxia, amino acid fluctuation, inflammation, and hormonal dysregulation [10, 42]. Protein aggregates induce ER stress and may eventually overwhelm the capacity of the unfolded protein response (UPR) and clearance

machineries, leading to deposition and accumulation of these aggregates in trophoblasts, extracellular domains and subsequently causing placental toxicity, poor trophoblast invasion, differentiation, superficial endometrial invasion and failure of spiral artery remodeling. Continuous accumulation of protein aggregates may aggravate ER stress and cause cell apoptosis, leading to release of aggregates into maternal circulation and excretion through injured glomerulus into urine.

ER stress is intricately linked to oxidative stress and inflammation, indicating the co-existence of these pathways in major pathologies particularly early on-set PE, through feed-forward mechanisms [43]. ER stress induction and UPR activation was insignificantly evident in both intra uterine growth retardation (IUGR) and IUGR associated early-onset pre-eclampsia (IUGR + PE) placentas. However, increased apoptosis, higher levels of eIF2 α phosphorylation, GRP94 and CHOP in the syncytiotrophoblast and endothelial cells of the foetal capillaries was evident in IUGR + PE placental samples and not in IUGR alone [44]. ER stress associated proteins such as GRP78, GRP94, p-PERK, eIF2 α , p-eIF2 α , XBP1, CHOP, IRE1, p-IRE1 and inducible nitric oxide synthase (NOS) expression were high in preeclamptic placentas compared to control placenta [45]. Overexpression of placental UPR pathways including IRE1, ATF6 and XBP-1 was significantly observed in early-onset PE compared to that of late-onset of PE and normotensive controls [33]. Preeclamptic placentas feature higher levels of ER stress with prominent activation of pro-inflammatory pathways that contributes to maternal endothelial cell activation. This complexity of cellular responses to ER stress emphasizes the need for a holistic approach for designing potential therapeutic interventions for PE. Antioxidants, ER chaperones, NO donors, statins and H₂S donors display pleiotropic antioxidant, anti-inflammatory, and pro-angiogenic effects on the signaling pathways involved in the pathophysiology of PE, exhibiting potential strategies for therapeutic intervention [46].

6. ER chaperones

The transcriptional up-regulation of ER chaperones is the hallmark of the ER stress response and occurs in all eukaryotic organisms. The primary function of ER resident chaperones and their cofactors involved in the ER quality control system is to monitor the error-prone steps in protein synthesis and assembly [13, 47]. Three major chaperone families exist in the ER that interact with a wide variety of clients: the lectin chaperones, which generally recognize incompletely folded glycosylated proteins, the heat shock proteins (HSPs) family, which interacts with both nonglycosylated as well as glycosylated proteins and the thiol oxidoreductases, that aids in the disulphide bond formation [48].

6.1 Heat shock proteins (HSPs)

HSPs are a large family of evolutionarily conserved molecular chaperones, first observed as a group of proteins upregulated in heat-stressed *Drosophila melanogaster* [49], that are well-known for their roles in protein maturation, re-folding and degradation. These molecular chaperones of this HSP family are critical effectors of the UPR adaptive response. They protect intracellular proteins from misfolding or aggregation, inhibit cell death signaling and preserve the intracellular signaling pathways that are essential for cell survival. HSPs classified according to their molecular weight as proteins of approximately 84 and 70 kDa (HSP84 and HSP70), are amongst the most prominent chaperones in the ER [50]. HSPs are constitutively expressed, inducibly regulated to prevent aggregation of misfolded polypeptides and assists in refolding, besides being crucial modulators of neurotoxicity in Alzheimer's

disease [51]. Placental ischemia, oxidative stress, maternal systemic inflammatory response are major elements in the pathogenesis of PE that induces the expression of HSP70 which in-turn is associated with cytokine aggravation, oxidative stress and hepatocellular injury [52].

Binding immunoglobulin protein (BiP)/glucose-regulated protein 78 (GRP78), belongs to the HSP70 family, is a well known ER chaperone that binds to the hydrophobic region of unfolded proteins. GRP78 binds through substrate-binding domain and assists protein folding through a conformational change, achieved through the hydrolysis of ATP by the ATPase domain. Another chaperone, oxygen-regulated protein (ORP)150/GRP170 belonging to the HSP110 family (a HSP70 subfamily), assists the protein folding similar to that of BiP. The group of ER DnaJ proteins-ERdj1, ERdj3/HEDJ, ERdj4, ERdj5, SEC63 and p58IPK belonging to the HSP40 family acts as co-chaperones, mediating the activity of BiP by regulating its ATPase activity [53, 54].

Hsp90 is an essential component of cytoplasmic Hsp90-Hsp70 chaperone network, responsible for protein folding. Protein emerging from ribosome is initially folded in nascent polypeptide by Hsp70 and then passed to the Hsp90 for later folding. GRP94, the hsp90 family chaperone, hydrolysis the ATP, facilitates protein folding and liable for the maturation of certain oligomeric proteins including Toll-like receptors (**Table 1**) [58].

Chaperone family	ER chaperone	Function
Heat shock proteins		
	GRP78/BiP	Facilitates folding and assembly of proteins, translocates the newly synthesized polypeptides, targets misfolded proteins for ERAD, regulates calcium homeostasis [27].
	GRP94/endoplasmic	Directs the oxidative folding and assembly of several secreted and membrane proteins that mainly contain disulphide bonds.
Lectin chaperones		
	Calnexin	Transmembrane protein binds to glycan residues of nascent polypeptides found in membrane proximal domains and retains substrate proteins in the ER until they are fully mature and their intermediate oligosaccharide is cleaved by glucosidase II [55].
	Calreticulin	Soluble luminal homolog associates with glycans within the ER lumen and interacts with monoglucosylated glycans, trimmed intermediates of N-linked core glycans on nascent glycoproteins [56].
Thiol oxidoreductases		
	ERp57/PDIA3	Participates in the folding of numerous cysteine-rich glycoproteins as an element of the CNX/CRT cycle [55].
	PDI/PDIA1/P4HB	Assists in redox protein folding via oxidation, multiple thiol-disulphide exchanges, isomerization, reduction activities and is highly specific in its interaction with different substrates [57].
	ERdj5	Catalyzes the removal of non-native disulfides by binding with BiP and ensures the correct folding of proteins entering the secretory pathway or dislocates misfolded proteins to the cytosol for degradation [54].

Table 1.
Classification of ER chaperones and their functional roles.

6.2 Lectin chaperones

A unique aspect of the ER involves glycosylation-assisted folding which is largely mediated by ER resident lectins. There are two calcium-activating chaperones in the ER - calnexin (CNX) and calreticulin (CRT), that associates with glycoproteins and completes the protein folding process [55, 59]. The CNX/CRT cycle is critical part of the ER quality control machinery in monitoring the glycosylation and sugar chain structures in protein folding and assembly. When one glucose residue is attached to the client protein, ER lectins bind to initiate the folding process and later release the protein to UDP-glucose-glycoprotein glucosyltransferase. The disulfide bond isomerase ER protein 57 (ERp57) majorly involved in the CNX/CRT cycle, catalyzes the oxidation and isomerization of the disulfide bonds in glycoproteins. Further, CRT elicits an immune response through the assembly of major histocompatibility complex (MHC) class I molecules for eventual antigen presentation on the cell surface, intended for apoptosis [60].

6.3 Thiol oxidoreductases

Formation of transient disulfide bonds in the protein folding process are mediated by thiol oxidoreductases and are essential for the activation of the PERK pathway [56]. These are the major proteins that redox control by utilizing catalytic cysteine residues for oxidation or reduction of their substrates. Protein disulphide isomerase (PDI), ERp72, ERp61, GRP58/ERp57, ERp44 and ERp29 are enzymes that mediate the formation of disulphide bonds through oxidizing cysteine residues of nascent proteins. However, most of the thioloxydoreductases act as oxidants [61] and in certain cancer models, ERp57 as well as PERK gets activated in a PDI dependent manner, reducing cancer cell proliferation and sensitizes cancer cells to ionizing radiation [62].

Hsp47 (Serpine H1) is an ER-resident collagen-specific molecular chaperone that is essential for molecular maturation of collagen. Hsp47 binds Yaa-Gly-Xaa-Arg-Gly in triple-helical procollagen in the ER via hydrophobic and hydrophilic interactions. The binding of Hsp47 stabilizes procollagen by preventing unfolding of the triple helix and aggregate formation. Thus, Hsp47 is indispensable for efficient secretion, processing, fibril formation, and deposition of collagen in the extracellular matrix [63]. The chaperone function of Hsp47 is also involved in the deterioration of fibrosis, suggesting Hsp47 as a therapeutic target for fibrotic diseases, including liver, lung and spleen fibrosis. Lipase maturation factor 1 (LMF1) is an ER chaperone that affects ER lipid metabolism through the activation of lipoprotein, hepatic and endothelial lipases [64]. Mutations in LMF1 are associated with severe hypertriglyceridemia caused by deficiency of these lipases.

7. Conclusion

Preeclampsia is the most frequently encountered medical complication in pregnancy that affects 3–7% of pregnant women worldwide, characterized by de novo on-set of hypertension, proteinuria after 20 weeks of gestation, entailing the heterogeneous etiological disease manifestations. Placental dysfunction due to reduced perfusion, trophoblast remodeling, oxidative stress, ER stress and exaggerated inflammatory response are the major factors that contributes to early on-set preeclampsia. Numerous reports substantiate that ER stress, protein misfolding and aggregation are the major inducers behind the etiological manifestations of PE, leading to disease pathogenesis [65, 66]. Furthermore, amyloid fibrous protein

aggregates are an emerging biomarker of PE representing amyloid aggregation of amyloid β , transthyretin, immunoglobulin light chains and alpha-1 antitrypsin. These aggregated proteins mediate defective trophoblast invasion and abnormal remodeling of spiral arteries leading to the onset of PE. This unveils new strategies to identify novel biomarkers as well as targets for therapeutic intervention, to alleviate the underlying pathological conditions and decrease the risk of preeclampsia.

Conflict of interest

The authors declare no conflict of interest.

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